Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 62, No. 6, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.04.038

EDITORIAL COMMENT

Preserve the Brain

Primary Goal in the Therapy of Atrial Fibrillation*

Eric N. Prystowsky, MD, Benzy J. Padanilam, MD

Indianapolis, Indiana

Treatment of atrial fibrillation (AF) involves 3 major strategies: prevention of stroke, maintenance of sinus rhythm, and rate control (1). Stroke is the most dreaded complication of AF, and its prevention is key. Anticoagulation with warfarin and the newer agents dabigatran, rivaroxaban, and apixaban is highly effective in preventing strokes in patients with AF (1–4). However, defining the appropriate patient for anticoagulant therapy is not an exact science, and the stroke risk schema $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke/transient ischemic attack) and CHA_2DS_2-VASc (Vascular disease, Age 65–74 years, [female] Sex category) have only modest predictive ability (5). Unfortunately, stroke

See pages 525 and 531

is not the only neurological consequence of AF. Cognitive impairment and silent cerebral infarcts (SCIs) without clinical strokes have been reported in patients with AF. Kilander et al. (6) showed that AF was associated with low cognitive function in elderly men independent of stroke. Further, memory impairment and hippocampal atrophy were identified in a group of stroke-free patients with AF and a mean age of 60 years (7). Bunch et al. (8,9) demonstrated that AF was independently associated with Alzheimer's disease and other forms of dementia, with the greatest risk in those ≤70 years of age. There is also a greater rate of decline in Alzheimer's disease with AF (10). Population studies appear to show that diabetes mellitus, a disease associated with a high risk of stroke, is an independent risk factor for AF, adding another variable to affect neurological function (11,12). Although patients undergoing ablation for AF have been reported to have lower risks of death and dementia than those without ablation (9), ablation itself is associated with procedure-related strokes (13) as well as silent cerebral embolic lesions detected by magnetic resonance imaging (MRI) (14–16). Lastly, AF is often asymptomatic but may have a significant stroke risk (1,17–20).

Two studies in this issue of the *Journal* (21,22) provide significant new insights on the effect of AF on more subtle neurological problems. Marfella et al. (21) evaluated the prevalence of subclinical AF and its relationship to SCI and stroke in otherwise healthy diabetic patients younger than 60 years of age. Asymptomatic AF episodes were discovered using intermittent 48-h Holter monitors quarterly in the first year and annually for another 3 years of follow-up. MRI of the brain was performed at baseline to evaluate for SCI. In total, 465 of 1,992 patients met the study criteria. Patients who developed clinical AF during follow-up were excluded; thus, any AF in the study group was subclinical and identified only as a result of the Holter monitoring. After an average follow-up of 37 months, 176 of 465 diabetic patients had silent episodes of AF (SAFE group). The prevalences of SCI (61% vs. 29%; $p < 0.01$) and stroke (17.3% vs. 5.9%; $p < 0.01$) were significantly higher in this group compared with diabetic patients without silent episodes of AF (non-SAFE group, $n = 288$). The mean duration of AF was 21 ± 15 h, and the absolute burden of AF correlated to the number and size of SCIs. The study also compared these diabetic patients with 240 nondiabetic case controls. The prevalences of silent AF and SCIs were very low, at 1.5% and 0.5%, respectively, in the control group. By design, therapeutic options were not evaluated. It is unclear from this report why a much lower percent of patients in the entire diabetic cohort (212 of 1,992; 11%) had silent AF compared with those who met the study criteria (176 of 465; 38%). A flowchart of patient selection would have helped with clarity. Despite these methodological drawbacks, the study findings are rather startling. First, brief asymptomatic episodes of AF occur frequently in diabetic patients. The 11% incidence of subclinical AF in the study, while already high, is almost certainly an underestimation due to the intermittent nature of the monitoring for arrhythmia. Second, subclinical AF events are associated with a high prevalence of SCI and subsequent development of stroke. Although the high prevalence of SCIs in the SAFE group may be readily attributed to AF, the non-SAFE group also had a relatively high prevalence of SCIs. Thus, many of the SCIs could be unrelated to AF events in either population or the study failed to detect AF events in the non-SAFE group.

In the second report, Medi et al. (22) evaluated whether post-procedural cognitive dysfunction (POCD) occurs after radiofrequency catheter ablation (RFA) of AF. Patients undergoing RFA for paroxysmal AF ($n = 60$) and persistent AF ($n = 30$) were compared with 30 patients undergoing RFA for supraventricular tachycardia (SVT), 7 of whom underwent a left atrial procedure, and 30 control patients with AF awaiting RFA. A trans-septal approach was used to access the left atrium. In patients undergoing anticoagulation

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily reflect the views of *JACC* or the American College of Cardiology.

From the St. Vincent Medical Group, St. Vincent Hospital, Indianapolis, Indiana. Dr. Prystowsky is a consultant and has received honoraria from Medtronic; is a member of the board of directors with fees and stock options for Stereotaxis and CardioNet; and holds stock in Topera. Dr. Padanilam holds stock in Topera.

therapy before ablation for AF, warfarin was stopped 5 days before the procedure and full-dose enoxaparin was given. After ablation, enoxaparin was continued until warfarin was therapeutic. All ablations were performed with the patient under general anesthesia, and there was no difference in the depth of anesthesia among the patient groups. Importantly, there was no evidence of clinical stroke after any of the ablations, although MRI studies to evaluate for SCI were not performed. Neuropsychological testing to determine POCD included 8 tests from the Canadian Study of Health and Aging and was conducted by a trained interviewer. The number of correct answers or the time taken to complete the test composed the results. The test was given 3 times: at baseline within 7 days before the procedure, 24 to 48 h after the procedure, and 3 months after the procedure. Analysis of the test scores used the reliable change index, and POCD was defined as a score of less than −1.96 on 2 tests or more and/or a combined z score of less than −1.96.

Patients with left-sided SVT had shorter left atrial access time and RFA time than did patients with AF. POCD was assessed 36 ± 10 h after RFA and at 39 ± 18 h in the AF control group. The incidence of POCD was 28%, 27%, and 13%, respectively, in the paroxysmal AF, persistent AF, and SVT groups. No deterioration was noted in any of the control patients. At the 3-month post-operative assessment, POCD was present in 13%, 20%, and 3% of patients with paroxysmal AF, persistent AF, and SVT, respectively. The incidences of POCD did not differ between the paroxysmal and persistent AF groups.

It has been well recognized for many years that cognitive decline can occur after coronary artery bypass surgery (23). However, data showing cognitive impairment after ablation for AF are disturbing and require further investigation (22,24). It will be important for future studies of POCD to incorporate MRI to determine whether SCI is associated with cognitive impairment, although it was not in one small study (24). It is unclear if performing ablations for AF with therapeutic warfarin anticoagulation would reduce the incidence of POCD. Different forms of ablation and anticoagulation strategies need to be evaluated to determine their comparative effect on POCD.

These 2 studies raise several important new questions. If the neurological sequelae of AF are not limited to stroke, have we omitted an important endpoint in the current state of AF management? Studies of anticoagulation in AF have only addressed endpoints of strokes and systemic embolization and not SCI or cognitive deterioration. In fact, it is possible that anticoagulation itself may lead to cerebral microhemorrhages and neurological dysfunction. Future studies of AF should evaluate SCI and cognitive dysfunction as end points.

How can we reduce the harmful neurological effects of AF in our patients? In our opinion, it will take a multipronged approach that includes re-evaluation of the safety of the rate control approach to AF. The apparent safety of this treatment strategy is based mainly on the results of the AFFIRM and RACE trials (25,26), which compared pharmacological rate control with rhythm control. The age of the patient populations studied was narrow (mean of 69.7 and 68 years, respectively), and the follow-up time was only a mean of 3.5 and 2.3 years, respectively. More recent data from a population-based database showed that patients treated with rhythm control drugs had reduced mortality when the follow-up was extended beyond 4 years (27). Using this same database, Tsadok et al. (28) concluded that patients treated with rhythm control drugs, especially those with a $CHADS_2$ risk of ≥1, had lower rates of stroke/transient ischemic attack with a similar number of patients treated with anticoagulation in the rate and rhythm control groups. Thus, we believe that the long-term safety of persistent AF has not been definitively established, especially in younger patients. The lack of outcomes data on neurocognitive function and SCIs should be considered when a rate control strategy is used in patients with AF.

We also need to identify patients with silent AF and a significant stroke risk, for example, the elderly or those with hypertension or diabetes, with the hope that appropriate anticoagulation will reduce the incidences of stroke and TIA. At present, monitoring using pacemakers or defibrillators (17,18), Holter monitors, or handheld recorders (19,21,29) may provide such information in some patients. Hopefully, consumer-friendly and cost-effective long-term electrocardiographic monitors will be readily available in the primary care setting to monitor specific patient populations for subclinical AF. At present, it is not known whether prescribing anticoagulants to patients with silent AF at high risk for stroke will reduce that risk, and randomized trials are needed to answer this important question. Detection of AF in such patients will allow the physician to discuss the relative merits of such therapy for each patient. Although ablation therapy appears to reduce some of the complications of AF (9), it is also associated with stroke, SCI, and POCD, and more research is needed to determine methods to reduce these risks.

In summary, we must do more to identify asymptomatic AF and evaluate new strategies to fulfill the first commandment of therapy for patients with AF: preserve the brain.

Reprint requests and correspondence: Dr. Eric N. Prystowsky, St. Vincent Medical Group, 8333 Naab Road, Suite 400, Indianapolis, Indiana 46260. E-mail: enprysto@stvincent.org.

REFERENCES

1. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). J Am Coll Cardiol 2006;48:854–906.
2. Connolly SJ, Ezekowitz MB, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51.

3. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–91.
4. Granger CB, Alexander JF, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365: 981–92.
5. Poli D, Lip GYH, Antonucci E, Grifoni E, Lane D. Stroke risk stratification in a "real world" elderly anticoagulated atrial fibrillation population. J Cardiovasc Electrophysiol 2011;22:25–30.
6. Kilander L, Andren B, Nyman H, Lind L, Boberg M, Lithell H. Atrial fibrillation is an independent determinant of low cognitive function: a cross-sectional study in elderly men. Stroke 1998;29:1816–20.
7. Knecht S, Oelschlager C, Duning T, et al. Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. Eur Heart J 2008;29:2125–32.
8. Bunch TJ, Weiss JP, Crandall BG, et al. Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. Heart Rhythm 2010;7:433–7.
9. Bunch TJ, Crandall BG, Weiss P, et al. Patients treated with catheter ablation for atrial fibrillation have long-term rates of death, stroke, and dementia similar to patients without atrial fibrillation. J Cardiovasc Electrophysiol 2011;22:839–45.
10. Mielke MM, Rosenberg PB, Tschanz J, et al. Vascular factors predict rate of progression in Alzheimer disease. Neurology 2007;69: 1850–8.
11. Nichols G, Reinier K, Chugh S. Independent contribution of diabetes to increased prevalence and incidence of atrial fibrillation. Diabetes Care 2009;32:1851–6.
12. Huxley RR, Filion KB, Konety S, Alonso A. Meta-analysis of cohort and case-control studies of type 2 diabetes mellitus and risk of atrial fibrillation. Am J Cardiol 2011;108:56–62.
13. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Heart Rhythm 2012;9:632–96.
14. Gaita F, Caponi D, Pianelli MN, et al. Radiofrequency catheter ablation of atrial fibrillation: a cause of silent thromboembolism? Magnetic resonance imaging assessment of cerebral thromboembolism in patients undergoing ablation of atrial fibrillation. Circulation 2010;122:1667–73.
15. Siklody CH, Deneke T, Hocini M, et al. Incidence of asymptomatic intracranial embolic events after pulmonary vein isolation. J Am Coll Cardiol 2011;58:681–8.
16. Haeusler KG, Koch L, Herm J, et al. 3 Tesla MRI-detected brain lesions after pulmonary vein isolation for atrial fibrillation: results of the MACPAF study. J Cardiovasc Electrophysiol 2013;24:14–21.
17. Botto GL, Padeletti L, Santini M, et al. Presence and duration of atrial fibrillation detected by continuous monitoring: crucial implications for the risk of thromboembolic events. J Cardiovasc Electrophysiol 2009; 20:241–8.
18. Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med 2012;366:120–9.
19. Engdahl J, Andersson L, Mirskaya M, Rosenqvist M. Stepwise screening of atrial fibrillation in a 75-year old population. Circulation 2013;127:930–7.
20. Hindricks G, Piorkowski C, Tanner H, et al. Perception of atrial fibrillation before and after radiofrequency catheter ablation: relevance of asymptomatic arrhythmia recurrence. Circulation 2005;112:307–13.
21. Marfella R, Sasso FC, Siniscalchi M, et al. Brief episodes of silent atrial fibrillation predict clinical vascular brain disease in type 2 diabetic patients. J Am Coll Cardiol 2013;62:525–30.
22. Medi C, Evered L, Silbert B, et al. Subtle post-procedural cognitive dysfunction after atrial fibrillation ablation. J Am Coll Cardiol 2013;62: 531–9.
23. Newmann MF, Kirchner JL, Phillips-Bute B, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med 2001;344:395–402.
24. Schwarz N, Kuniss M, Nedelmann M, et al. Neuropsychological decline after catheter ablation of atrial fibrillation. Heart Rhythm 2010; 7:1761–7.
25. The Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002; 347:1825–33.
26. Van Gelder IC, Hagens VE, Bosker HA, et al. Comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med 2002;347:1834–40.
27. Ionescu-Ittu R, Abrahamowicz M, Jackevicius CA, et al. Comparative effectiveness of rhythm control vs rate control drug treatment effect on mortality in patients with atrial fibrillation. Arch Intern Med 2012;172: 997–1004.
28. Tsadok MA, Jackevicius, Essebag V, et al. Rhythm versus rate control therapy and subsequent stroke or transient ischemic attack in patients with atrial fibrillation. Circulation 2012;126:2680–7.
29. Saxon LA. Ubiquitous wireless ECG recording: a powerful tool physicians should embrace. J Cardiovasc Electrophysiol 2013;24: 480–3.

Key Words: ablation ■ atrial fibrillation ■ neurocognitive dysfunction ■ outcomes.